Fat distribution in HIV-infected patients reporting truncal enlargement quantified by whole-body magnetic resonance imaging\(^1\)–\(^3\)

Ellen S Engelson, Donald P Kotler, YanXiu Tan, Denise Agin, Jack Wang, Richard N Pierson Jr, and Steven B Heymsfield

**ABSTRACT**

**Background:** Antiretroviral therapy has improved the prospects for people infected with HIV, but some develop a syndrome of profound body habitus and metabolic alterations that include truncal enlargement.

**Objective:** The purpose of this study was to define the body-composition changes associated with this syndrome by using techniques with the power to estimate regional body composition.

**Design:** We compared whole-body and regional skeletal muscle and adipose tissue contents measured by magnetic resonance imaging and dual-energy X-ray absorptiometry (DXA) in 26 HIV-infected patients and 26 matched control subjects. Twelve of the HIV-infected patients had evidence of truncal enlargement.

**Results:** HIV-infected men and women who noted truncal enlargement had similar amounts of skeletal muscle and subcutaneous adipose tissue but greater visceral adipose tissue than HIV-infected patients without truncal enlargement; these values were larger in men (\(P < 0.001\)) than in women (\(P = 0.08\)). The ratio of visceral to subcutaneous adipose tissue was greater in both men (\(P < 0.02\)) and women (\(P = 0.05\)) with truncal enlargement. Two subjects with MRI-confirmed visceral adiposity syndrome (VAS) were not taking protease inhibitors. CD4\(^+\) lymphocyte counts were higher (\(P < 0.001\)) and plasma viral burdens tended to be lower (\(P = 0.08\)) in HIV-infected patients with VAS.

**Conclusions:** There was significantly more visceral adipose tissue in the subgroup of HIV-infected patients with truncal enlargement than in those without this sign. VAS occurs in both men and women, is associated with higher CD4\(^+\) lymphocyte counts and lower plasma HIV viral burdens, and is not limited to those receiving protease inhibitor therapy. *Am J Clin Nutr* 1999;69:1162–9.

**KEY WORDS**

Adipose tissue, regional fat distribution, nutrition assessment, HIV infection, antiretroviral agents, protease inhibitors, magnetic resonance imaging, MRI, densitometry, dual-energy X-ray absorptiometry, DXA, body composition, visceral adiposity syndrome, syndrome X, truncal enlargement, body cell mass, humans

**INTRODUCTION**

Alterations in nutritional status and metabolism are common in HIV infection and may be a direct consequence of the underlying HIV infection or secondary to disease complications. Our earliest body-composition studies showed severe weight loss and body cell mass (BCM) depletion in people with AIDS and secondary infections (1, 2). Other investigators subsequently found BCM depletion without weight loss in intermediate-stage HIV-infected men (3) as well as elevated resting energy expenditures in asymptomatic HIV-infected patients (4). Direct relations between plasma HIV RNA content and resting energy expenditure (5) and between plasma HIV RNA content and a history of weight loss (6) have been described. Therefore, the reduction in HIV content in plasma and lymphoid tissues accomplished with recent advances in antiretroviral therapies, including protease inhibitors, could be expected to generate nutritional effects.

Several studies documented inconsistent weight gain after initiation of antiretroviral therapies (7, 8) and there are emerging reports of other unusual or distinctive nutritional alterations. In HIV-infected men treated with protease inhibitors, dual-energy X-ray absorptiometry (DXA) showed fat loss in all regions except the trunk (9). Single-slice abdominal computed tomographic scans in 30 HIV-infected men showed greater visceral adipose tissue in some men treated with the antiretroviral protease inhibitor indinavir than in untreated men with similar BMIs (10). The change in fat distribution is sometimes accompanied by a prominent dorsocervical fat pad (“buffalo hump”) (11) and metabolic alterations that may include hyperlipidemia, insulin resistance, and diabetes mellitus (9). The observed body habitus is suggestive of Cushing syndrome, but serum cortisol concentrations are typically normal and cortisol secretion is normally suppressed by dexamethasone (11). A similar constellation of signs and symptoms has been identified in non-HIV-infected individuals and is termed syndrome X (12). Clinical studies associate syndrome X with...
with adverse health outcomes, predominantly related to type 2 diabetes and cardiovascular disease (13, 14).

The primary purpose of this study was to define the regional body-composition changes in HIV patients reporting truncal enlargement. We asked the following specific questions: Does total-body skeletal muscle or fat differ in HIV-infected patients and control subjects? Is fat distribution altered between the subcutaneous and visceral compartments in cases of truncal enlargement? Are the changes similar in men and women? Among HIV-infected patients, are the changes limited to those patients reporting truncal enlargement? Are there any differences in antiretroviral medications, viral load, CD4+ lymphocyte counts, exercise training, or steroid hormone use between HIV-infected patients with and without the body-composition changes characterized by this study?

SUBJECTS AND METHODS

Study design

This was a prospective, cross-sectional study performed as part of a Program Project Grant designed to develop and apply methods for the accurate estimation of adipose tissue and skeletal muscle mass. HIV-infected patients and healthy control subjects were recruited for separate investigations in the study, but all had the same body-composition studies performed. The studies were approved by the Institutional Review Board of St. Luke’s–Roosevelt Hospital Center.

Subjects

Twenty-six HIV-infected patients (15 men and 11 women) were matched with healthy, control subjects by sex, race, age (±5 y), and height (±10 cm). Control subjects were not tested for HIV infection. When there was more than one possible match from the database of 266 control subjects (147 women and 119 men) on the basis of these criteria, the control subject whose weight was the closest to the subject’s was used. Because a case definition for the presence of a lipodystrophy or visceral adiposity syndrome (VAS) in HIV has not yet been formulated, cases of truncal enlargement were identified by self-report of changes in body shape, including increased abdominal girth (ie, protuberant abdomens), that were confirmed on physical examination. Seven male and 5 female HIV-infected patients with truncal enlargement, with or without weight gain, were identified.

Body-composition measurements

Body weight was measured to the nearest 0.1 kg (Weight Tronix, New York) and height to the nearest 0.5 cm by using a stadiometer (Holtain, Crosswell, United Kingdom). Total skeletal muscle and total, visceral, and subcutaneous adipose tissue mass were measured by using magnetic resonance imaging (MRI)–derived cross-sectional images of the total body (15–17). Subjects were placed on the 1.5T scanner (6X Horizon; General Electric, Milwaukee) platform with their arms fully extended above their heads. The protocol involved the acquisition of ∼40 axial images of 10-mm thickness at 40-mm intervals from head to toe (16, 17). All MRI scans were analyzed by the same observer, who manually identified and quantitated adipose and lean tissue compartments with VECT image analysis software (Martel, Inc, Montreal) on a Silicon Graphics Workstation (Mountain View, CA). Cross-sectional areas on each image were integrated to provide volume estimates for the whole body and compartments by using the following equation:

\[
\text{Volume (L)} = 0.001 \times A \times (B_1 + B_2)/2
\]

where \(A\) is the distance (cm) between scans and \(B_1\) and \(B_2\) are tissue areas (cm²) in adjacent scans (15). Data are expressed as volume of skeletal muscle or adipose tissue. The difference in results on repeated measurements in our laboratory averages 0.7% for skeletal muscle and 1.1% for adipose tissue (18).

Total body fat and fat-free mass (composed of lean soft tissue and bone mineral) were measured with a whole-body DXA scanner (version 3.6 software, DPX; Lunar Radiation Corp, Madison, WI) (19). Regional measurements were made by using system defaults that outline appendages and trunk, and appendicular lean soft tissue results were used to estimate appendicular skeletal muscle (20). The difference for repeated measurements in our laboratory for DXA averages 1.2% for fat-free body mass and 4.7% for fat (21).

\(^{40}\text{K}\) was measured by using a 4-pi whole-body counter (22) over 9 min and the results were adjusted for body size by using a \(^{40}\text{K}\) calibration equation (23). The difference for repeated measurements in our laboratory is ±2.4% (21). Total body potassium (TBK; in mmol) was derived from \(^{40}\text{K}\) counts, and BCM (in kg) was calculated as TBK \(\times 0.00833\) (24).

Blood measurements

Peripheral blood CD4+ lymphocyte counts and plasma HIV RNA contents were determined in a clinical laboratory, the latter by reverse transcriptase–polymerase chain reaction.

Data analyses

Because of the significant effects of sex on normal body composition, men and women were analyzed separately. Comparisons of body-composition results in the HIV-infected patients and control subjects were performed by using paired \(t\) tests on matched patients and control subjects. Among HIV-infected patients, those reporting truncal enlargement were compared by the \(t\) test for independent samples with those not reporting truncal enlargement. A \(P\) value < 0.05 was considered significant.

The possible relation between truncal enlargement and other variables that could affect body composition was explored by comparing the frequency of occurrence in those with and in those without abdominal adiposity by Fisher’s exact test. The independent variables were antiretroviral medication; specific protease inhibitor use; megestrol acetate (Megace; Bristol-Myers Oncology Division, Princeton, NJ) and prednisone therapy, which are known to increase body fat (25, 26); use of known anabolic agents, including growth hormone, testosterone, and synthetic androgens; and participation in an exercise program. Because antiretroviral medications could affect body composition directly or indirectly—eg, through effects on HIV or on CD4+ lymphocytes—log-transformed plasma HIV RNA content (copies/L) and CD4+ count (cells/L) were compared by \(t\) test.

To determine the reliability of self-report of truncal enlargement for identification of cases of VAS, an analysis by Fisher’s exact test was performed by using the criteria for VAS of 2 SDs greater than the mean of the control group. Separate analyses were performed in which HIV-infected patients who reported truncal enlargement were compared with control subjects and with HIV-infected patients without truncal enlargement.
TABLE 1
Characteristics of HIV-infected patients and control subjects matched by race, age, and height

<table>
<thead>
<tr>
<th>Race or ethnic group</th>
<th>HIV-infected (n = 15)</th>
<th>Control (n = 15)</th>
<th>HIV-infected (n = 11)</th>
<th>Control (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>11</td>
<td>11</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3</td>
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<tr>
<td>Black</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Age</td>
<td>42.4 ± 6.7</td>
<td>43.0 ± 7.9</td>
<td>41.6 ± 5.1</td>
<td>41.2 ± 5.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178.8 ± 7.0</td>
<td>177.7 ± 7.1</td>
<td>158.9 ± 7.8</td>
<td>158.5 ± 6.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.4 ± 9.1</td>
<td>78.6 ± 7.5</td>
<td>56.8 ± 6.9</td>
<td>59.7 ± 11.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 ± 2.8</td>
<td>24.9 ± 1.9</td>
<td>22.5 ± 1.8</td>
<td>23.8 ± 4.5</td>
</tr>
</tbody>
</table>

\( \overline{x} \pm SD \)

1Significantly different from control men: \( P = 0.048, ^{2}P = 0.024 \).

RESULTS

HIV-infected patients compared with control subjects

HIV-infected patients and control subjects were similar in age and height, as expected from the matching procedure (Table 1). Weight and BMI were similar in HIV-infected and control women, but HIV-infected men weighed less and had BMIs (in kg/m²) that were significantly lower than their matched control subjects. There was a trend toward lower BCM for both HIV-infected men \( (P = 0.07) \) and women \( (P = 0.06) \) on the basis of TBK (Table 2). Significant differences in fat content by DXA existed for men \( (P = 0.06) \) and women \( (P = 0.048) \) on the basis of TBK. The ratio of visceral to subcutaneous adipose tissue was more than triple that of control subjects and the ratio of visceral to total adipose tissue was slightly more than double \( (P < 0.01) \) in HIV-infected men.

Subjects with compared with those without truncal enlargement

Among HIV-infected patients, the 7 men and 5 women reporting truncal enlargement were similar in height and weight to those not reporting truncal enlargement (Table 3). Women were also similar in age and BMI, but the men with truncal enlargement were significantly older \( (by \text{an} \ \text{average} \ \text{of} \ 7.5 \ \text{y}) \) and had a significantly greater BMI \( (by \ \text{an} \ \text{average} \ \text{of} \ 3.1) \) than those without truncal enlargement. However, the results in women must be viewed with the understanding that given a sample size of 11 subjects, we can only detect mean differences between groups that are \( \geq 2.5 \ \text{SDs} \) with 80% power.

BCM and total and regional skeletal muscle and lean tissue were similar between HIV-infected patients with and without truncal enlargement (Table 4). Among men, both subgroups had similar quantities of subcutaneous adipose tissue, but men with truncal enlargement had more total adipose tissue and 6.5 times more visceral adipose tissue than those without

TABLE 2

Body-composition measurements by TBK, DXA, and MRI by sex in HIV-infected patients and control subjects matched by race, age, and height

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected (n = 15)</th>
<th>Control (n = 15)</th>
<th>HIV-infected (n = 11)</th>
<th>Control (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body cell mass, by TBK (kg)</td>
<td>30.4 ± 7.0</td>
<td>32.1 ± 4.7</td>
<td>25.3 ± 7.0</td>
<td>26.9 ± 7.1</td>
</tr>
</tbody>
</table>

\( \overline{x} \pm SD \)

1Significantly different from control men: \( ^{2}P = 0.02, ^{3}P = 0.01, ^{4}P = 0.001, ^{5}P = 0.0008, ^{6}P = 0.04, ^{7}P = 0.007, ^{8}P = 0.03 \).
truncal enlargement (Figure 1). In women, total adipose tissue was similar in both subgroups, although women with truncal enlargement had 3 times more visceral adipose tissue with a trend toward being significantly different from women with no truncal enlargement ($P = 0.08$). In both men and women, the ratios of trunk fat to total fat by DXA, of visceral to subcutaneous adipose tissue, and of visceral to total adipose tissue by MRI were significantly higher in those with truncal enlargement.

Thus, HIV-infected patients reporting truncal enlargement had an abnormal distribution of body fat, shown by both DXA and MRI, compared with HIV-infected patients without truncal enlargement and with control subjects. The differences in adipose tissue distribution are evident in Figure 1 and Figure 2. Images of single-abdominal MRI scans taken in an HIV-infected subject with VAS and his matched control subject are shown in Figure 2. Although the limitations of the control database did not permit matching of all subjects based on weight and total adipose tissue content, these 2 variables were similar in the 2 subjects represented in these MRI scans. The plots in Figure 1 also illustrate the disparity based on HIV status between the ranges of subcutaneous and visceral adipose tissue contents. Ranges of total adipose tissue and subcutaneous adipose tissue contents were similar in HIV-infected patients and control subjects; the lesser influence of the visceral compartment on total adiposity was based on its smaller size.

Of the 25 HIV-infected patients whose medication status was known, 19 were taking antiretroviral medications, and of these, 17 were taking protease inhibitors. Ten of the 17 (59%) taking protease inhibitors had VAS. One woman with VAS had taken no anti-HIV medications and one man with VAS was taking antiretroviral medications but no protease inhibitor. Thus, 2 of 8 patients (25%) not taking protease inhibitors had VAS.

Mean (±SD) CD4+ lymphocyte cell counts averaged $86 ± 91 \times 10^6$ cells/L in the HIV-infected patients without VAS and $323 ± 155 \times 10^6$ cells/L in the HIV-infected patients with VAS ($P < 0.001$). The differences were similar in men and women ($P = 0.02$ for men and $P = 0.005$ for women). There was a trend toward a greater average log$_{10}$ plasma HIV RNA concentration in HIV-infected patients without VAS ($3.8 ± 0.9 \times 10^3$ copies/L) than in those with VAS ($3.1 ± 0.9 \times 10^3$ copies/L) ($P = 0.08$), and the difference became significant when an outlier value for one of the women with VAS and with a log viral load of $5.6 ± 10^3$ copies/L was eliminated from the statistical analysis ($3.8 ± 0.9$ compared with $2.8 ± 0.5 \times 10^3$ copies/L; $P = 0.007$). The difference in viral burden was significant in men ($3.8 ± 0.9$ compared with

**FIGURE 1.** Amounts of subcutaneous adipose tissue, visceral adipose tissue, and total adipose tissue, and the ratio of visceral (VAT) to subcutaneous adipose tissue (SAT) measured by magnetic resonance imaging in healthy, control subjects (●, men; ○, women) and in HIV-infected patients (HIV+) with (●, men; □, women) and without (▲, men; △, women) truncal enlargement. Horizontal lines represent means; thick, solid lines indicate control subjects; thin, solid lines indicate all HIV-infected patients; dashed lines indicate HIV-infected patients with truncal enlargement; and dotted lines indicate HIV-infected patients without truncal enlargement. 1,2 Significantly different from control men: 1 $P < 0.005$, 2 $P < 0.05$. 3,4 Significantly different from HIV-infected men without truncal enlargement: 3 $P < 0.001$, 4 $P < 0.02$. 5 Significantly different from HIV-infected women without truncal enlargement, $P = 0.05$. 

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2.7 ± 0.2 × 10^3 copies/L; \( P = 0.02 \)) but not in women (3.8 ± 1.1 compared with 3.6 ± 1.4 × 10^3 copies/L; \( P = 0.78 \)), even when the outlier was eliminated (\( P = 0.32 \)).

Use of hormonal agents known to affect body composition, such as megestrol acetate, prednisone, and anabolic agents, was infrequent in the HIV-infected patients (19% took one or more) and was not significantly different between those with and those without VAS (Table 5). Participation in an exercise program was similar between groups.

**Reliability of self-report for visceral adiposity syndrome**

There was a highly significant relation between self-report of truncal enlargement and a ratio of visceral to subcutaneous adipose tissue > 2 SDs above the mean of control subjects (Fisher’s exact test, \( P < 0.001 \)) or the mean of HIV-infected patients without self-report of truncal enlargement (\( P < 0.0001 \)). All HIV-infected men who reported truncal enlargement had ratios of visceral to subcutaneous adipose tissue > 2 SDs above the mean of both comparison groups. Only one HIV-infected man without self-report of truncal enlargement had a ratio > 2 SDs above the range for the control men, but within the range for HIV-infected men without truncal enlargement, and had a ratio of visceral to subcutaneous adipose tissue approximately half that of the male VAS patient with the next greatest ratio. Three male but no female control subjects had a ratio of visceral to subcutaneous adipose tissue > 2 SDs above the mean of the control group, but none of the male control subjects had ratios nearly as high as any of the HIV-infected men with VAS. Among women, there was more overlap in the range of ratios of visceral to subcutaneous adipose tissue. A separate analysis found only a trend toward significance in the relation between self-report of truncal enlargement and the incidence of a ratio of visceral to subcutaneous adipose tissue > 2 SDs above the mean of HIV-infected patients without self-report of truncal enlargement (\( P = 0.08 \)) and a nonsignificant relation compared with control subjects (\( P = 0.18 \)). Only 2 HIV-infected women, both of whom had VAS, had a ratio of visceral to subcutaneous adipose tissue > 2 SDs above the mean ratio of control women, although 4 of the 5 women with VAS had a ratio of visceral to subcutaneous adipose tissue > 2 SDs above the mean ratio of HIV-infected women without VAS. The fifth female subject with VAS was the only one who had a lower ratio than any woman without VAS. Thus, self-report of truncal enlargement appears to be generally reliable in predicting the MRI result for identification of VAS, but more so in men than in women.

**TABLE 3**
Characteristics of HIV-infected patients with and without report of truncal enlargement (TE)

<table>
<thead>
<tr>
<th>Race or ethnic group</th>
<th>TE ((n = 7))</th>
<th>No TE ((n = 8))</th>
<th>TE ((n = 5))</th>
<th>No TE ((n = 6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Age</td>
<td>46.4 ± 6.4^1</td>
<td>38.9 ± 5.4^2</td>
<td>44.0 ± 5.3</td>
<td>39.7 ± 4.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>176.3 ± 5.1</td>
<td>181.0 ± 8.1</td>
<td>162.0 ± 2.9</td>
<td>156.2 ± 9.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.5 ± 7.0</td>
<td>70.7 ± 10.3</td>
<td>59.1 ± 6.4</td>
<td>54.8 ± 7.3</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>24.6 ± 2.3</td>
<td>21.5 ± 2.5^1</td>
<td>22.5 ± 2.6</td>
<td>22.4 ± 1.0</td>
</tr>
</tbody>
</table>

^1x ± SD.
^2Significantly different from men with TE: ^3P = 0.023, ^4P = 0.027.

**TABLE 4**
Body-composition measurements by TBK, DXA, and MRI by sex in HIV-infected patients with and without report of truncal enlargement (TE)^1

<table>
<thead>
<tr>
<th></th>
<th>TE ((n = 7))</th>
<th>No TE ((n = 8))</th>
<th>TE ((n = 5))</th>
<th>No TE ((n = 6))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body cell mass, by TBK (kg)</td>
<td>30.5 ± 3.6</td>
<td>30.3 ± 5.7</td>
<td>18.6 ± 1.7</td>
<td>18.9 ± 3.0</td>
</tr>
<tr>
<td>Fat tissue, by DXA (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16.1 ± 4.9^1</td>
<td>9.2 ± 4.3</td>
<td>19.4 ± 7.7</td>
<td>16.5 ± 2.9</td>
</tr>
<tr>
<td>Arm</td>
<td>0.9 ± 0.4</td>
<td>0.7 ± 0.4</td>
<td>1.8 ± 1.0</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>Leg</td>
<td>2.6 ± 2.0</td>
<td>2.8 ± 1.7</td>
<td>6.3 ± 2.4</td>
<td>7.0 ± 2.1</td>
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<tr>
<td>Trunk</td>
<td>11.9 ± 2.6^1</td>
<td>5.2 ± 2.4</td>
<td>10.3 ± 4.3</td>
<td>7.3 ± 1.9</td>
</tr>
<tr>
<td>Trunk:total</td>
<td>0.75 ± 0.09^2</td>
<td>0.056 ± 0.07</td>
<td>0.53 ± 0.03^1</td>
<td>0.44 ± 0.07</td>
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<tr>
<td>Lean tissue, by DXA (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>58.6 ± 7.2</td>
<td>58.7 ± 10.1</td>
<td>37.2 ± 2.4</td>
<td>36.6 ± 5.8</td>
</tr>
<tr>
<td>Arm</td>
<td>6.6 ± 1.4</td>
<td>6.7 ± 1.5</td>
<td>3.7 ± 0.4</td>
<td>3.8 ± 0.4</td>
</tr>
<tr>
<td>Leg</td>
<td>19.4 ± 2.7</td>
<td>16.6 ± 6.9</td>
<td>11.3 ± 1.0</td>
<td>12.1 ± 1.9</td>
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<tr>
<td>Trunk</td>
<td>28.9 ± 3.4</td>
<td>29.2 ± 4.6</td>
<td>19.4 ± 1.3</td>
<td>17.9 ± 3.5</td>
</tr>
<tr>
<td>Skeletal muscle, by MRI (L)</td>
<td>29.7 ± 5.5</td>
<td>27.3 ± 6.3</td>
<td>17.1 ± 0.9</td>
<td>17.6 ± 3.0</td>
</tr>
</tbody>
</table>

^1x ± SD. TBK, total body fat potassium by ^2K counting; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging.
^2Significantly different from patients of the same sex without TE: ^3P = 0.015, ^4P = 0.0003, ^5P = 0.0009, ^6P = 0.0352.
DISCUSSION

The major finding of this study was excess visceral adipose tissue, with relatively little subcutaneous adipose tissue, in HIV-infected patients with truncal enlargement. Several techniques of varying sophistication are capable of assessing regional body composition. We used MRI (27), a cross-sectional imaging technique that, like computed tomography (28), provides both accurate and precise determinations of regional tissue compartments and definitively detects body-composition changes in HIV-infected people with truncal enlargement.

In this study, HIV-infected patients were matched with healthy control subjects on the basis of independent determinants of adipose tissue quantity and distribution. HIV-infected patients weighed less than control subjects, although the differences were significant only in men. The difference in weight between men was mainly in body fat, whereas the difference in weight between women was mainly in lean tissue. These results differ from those of earlier studies (1–3), which frequently included many clinically ill subjects, which did not match individual subjects to control subjects, and which cannot otherwise be compared with the present study, which is more limited to a specific clinical phenomenon. DXA showed less appendicular but not less truncal fat in HIV-infected men than in control subjects, as reported by others (9), whereas MRI showed less subcutaneous and more visceral fat in HIV-infected men. Because DXA cannot distinguish subcutaneous from visceral fat, less subcutaneous fat in the trunk masked more visceral fat; therefore, truncal fat by DXA appeared to be the same in HIV-infected patients as in control subjects. HIV-infected men also had less lean tissue in the legs and a trend toward less lean tissue in the arms by DXA than their matched control subjects, consistent with less total BCM by whole-body counting of 40K. There were no significant differences in total body or regional fat content between HIV-infected women and their matched control subjects, but there was a trend toward less BCM by TBK in the HIV-infected women, consistent with less skeletal muscle by MRI, and less appendicular skeletal muscle by DXA. Thus, both men and women had less appendicular skeletal muscle than control subjects.

Interpretation of the body-composition results was confounded by the subgroup of HIV-infected patients (46%) who noted a change in body habitus. A previous study validated self-report of anthropometric measures (29) and the current study confirms the general reliability of self-report as an indicator of body habitus. Both men and women with truncal enlargement had more adipose tissue than those who did not notice such a change, although the differences were significant only in men. The excess adipose tissue was located in the visceral compartment, whereas the subcutaneous adipose tissue compartments in men and women with and without truncal enlargement were similar and smaller than in the control subjects. Thus, depletion of subcutaneous adipose tissue appears to be a characteristic of HIV infection, irrespective of visceral adipose tissue accumulation.

The differences in visceral adipose tissue were larger in men than in women. The degree of this sex difference was consistent with that found in android obese men and women with similar BMIs (30). Ratios of visceral to subcutaneous adipose tissue by

TABLE 5

<table>
<thead>
<tr>
<th>VAS</th>
<th></th>
<th>No VAS</th>
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</thead>
<tbody>
<tr>
<td>Men (n = 7)</td>
<td>Women (n = 5)</td>
<td>Men (n = 8)</td>
<td>Women (n = 6)</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>1</td>
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<td>1</td>
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<tr>
<td>Prednisone</td>
<td>0</td>
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<td>Growth hormone</td>
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</tr>
<tr>
<td>Testosterone</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Other anabolic agents</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Exercise program</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

1Some subjects are represented more than once. There were no significant differences when data for men and women were combined and analyzed by Fisher’s exact test.
whole-body MRI, with use of methods similar to those in the present study, were 0.07 ± 0.03 in android obese women and 0.17 ± 0.10 in android obese men. Part of this sex difference may reflect changes in women in other fat depots, particularly mammary tissue, that have been reported as part of this syndrome (31) but were not measured in the present study. Of note, the patients with VAS in the present study, especially the men, had greater mean ratios of visceral to subcutaneous adipose tissue (Table 4) than the android obese individuals with the body habitus associated with the metabolic syndrome X. The absolute quantity of visceral adipose tissue in VAS is also unusually great. Compared with 221 control subjects from our institution for whom the quantity of visceral adipose tissue determined by MRI was available, and among whom the greatest volume was 7.3 L (in a 52-y-old man with a BMI of 30), 3 men with VAS had >8.5 L visceral adipose tissue. In a group of 17 male android obese subjects without HIV (30), the mean (±SD) was 4.8 ± 2.1 L visceral adipose tissue. Although we did not control for weight differences, doing so would make the excess VAT in VAS patients even more exceptional.

The temporal association between the recognition of patients with truncal enlargement and the application of protease inhibitor therapy has led several investigators to conclude that the change is related to protease inhibitor therapy (9, 10, 32; HE Rosenberg, J Mulder, KA Sepkowitz, MF Giordano, unpublished observations, 1998). However, a study of HIV-infected patients who had developed a buffalo hump found that one-half of the patients were not taking protease inhibitors (11). In the current study, 2 patients (17%) with truncal enlargement and visceral fat accumulation were not taking protease inhibitors, 1 of whom was not receiving any antiretroviral therapy. Combination antiretroviral therapy with or without protease inhibitors might have indirect effects on nutritional status that are related to viral suppression and improved health. In the present study, CD4+ lymphocyte counts were significantly higher in both men and women with truncal enlargement, who also showed a trend toward lower plasma HIV concentrations. In another larger study from this laboratory, plasma viral burden contributed significantly to the prediction by anthropometric measures of altered fat distribution, whereby a lower viral load predicted a greater waist-to-hip ratio and visceral adipose tissue area (33). Thus, the development of truncal adiposity, rather than being a direct effect of protease inhibitors, may be a response to the return toward health that these drugs promote. The results of these studies do not mean that VAS is related to earlier-stage HIV illness. Although the nadir of CD4+ lymphocyte cell counts and pretreatment plasma HIV viral contents were not available for analysis, highly active antiretroviral therapies increase CD4+ counts and decrease viral loads in a significant proportion of patients (34). The results of this study do not rule out a significant direct effect of protease inhibitors on body composition.

There is a growing consensus that truncal enlargement in HIV-infected patients is associated with multiple metabolic abnormalities, including insulin resistance with or without diabetes mellitus, hypertriglyceridemia, and hypercholesterolemia. Although the changes in body habitus suggest Cushing syndrome, morning serum cortisol concentrations are typically normal and dexamethasone suppression tests successfully suppress cortisol secretion (11). However, the absence of Cushing syndrome does not prove normal adrenocortical function. Although serum and urine analyses were not available for the groups in the present study, 2 of the subjects with truncal enlargement had buffalo humps, 1 of whom also had bulging supraclavicular fat pads. We found elevated 24-h urinary cortisol secretion in several subjects with truncal enlargement in another study (33), whereas studies from different laboratories found both normal and elevated 24-h urinary free cortisol excretion in similar subjects (11, 35). Of relevance, the etiology of syndrome X is obscure, but may include an exaggerated stress response including chronic mild hypercortisolism (36).

Other causes of increased visceral adiposity include testosterone deficiency (37) and adult growth hormone deficiency (38). The serum testosterone concentration was not measured in this study. We found no differences in the use of these anabolic agents in subjects with or without visceral adiposity, nor were differences noted in the use of corticosteroids, megestrol acetate, or resistance exercise training. Thus, it appears that these variables do not effect the occurrence of VAS. However, the small group sizes mean we only have 80% power to detect mean differences between groups that are equivalent to ≥1.28 SDs, making it difficult to make a definitive statement on the basis of this study.

The implications of HIV-associated VAS are uncertain, but because the findings related to body composition and metabolism in VAS are similar to those in syndrome X (12) and because epidemiologic studies associate syndrome X with a high risk for type 2 diabetes and premature vascular disease development (13, 14, 39, 40), it is notable that a report by Seidell et al (41) describes angina and coronary artery occlusion in 2 young HIV-infected men treated with protease inhibitors.

Further study of HIV-associated VAS is required to determine its mechanisms and outcomes. The relation of VAS to protease inhibitor therapy remains unclear, as does a complete case definition of the syndrome. In particular, the different presentations in men and women could be further defined and the relation between the body-composition changes and metabolic abnormalities should be determined. Furthermore, it remains to be ascertained whether the body-composition and metabolic changes represent a significant health risk and whether any potential risks could be prevented through medical, nutritional, or exercise intervention.

REFERENCES